

stream smoke (e.g., increased concentration of chemicals or decreased particle size), it would be difficult to detect by comparing smokers to nonsmokers when the nonsmoking group also includes passive smokers. Alternatively, one could speculate that smokers, although at increased overall risk, may paradoxically be protected against some properties of cigarette smoke, possibly through stimulation of enzyme systems that metabolize carcinogens into less harmful compounds (13, 14). These same mechanisms may not be stimulated in nonsmokers who have different exposure to cigarette smoke.

We would not want to argue that a biologic pathway is established, but rather to say that a plausible pathway cannot be ruled out. Evidence suggests that passive smoking is not simply a lower dose of active smoking, and thus may need to be considered in a different light. Our findings are preliminary and need to be confirmed by other studies. Studies of individual cancer sites can evaluate potential confounding factors in more detail, and may be able to clarify the role of passive smoking.

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smokers, then we are contrasting families with a single smoker against families where neither spouse smokes. And differences could exist between them. Thus we might ask: 1) Are their alcohol consumption habits the same? 2) What are the differences in their dietary habits? 3) How might they differ in age at first intercourse, frequency of intercourse, circumcision status of husband, etc.? 4) Are numbers of children or pregnancies and ages at first birth or pregnancy the same for single-smoker and nonsmoker families? 5) What true differences may exist in occupations leading to cancer?

These possible correlates of smoking practice might account for the observed differences reported in cancers of a variety of sites, and these are the true potential confounding factors, whether or not we are in a position to get at them. What Sandler et al. have taken as potential confounding factors are just the straightforward factors requiring adjustment that any reasonable epidemiologist would employ.

One particular thing strikes me about the Sandler et al. study. Passive smoking has been shown to double the risk of all cancers among nonsmokers, albeit true confounding factors have not been taken into account. But studies focusing on lung cancer among nonsmokers

consequent on passive smoking have also come up with about the same doubling of risk. To other criticisms made of such other studies may be added that they may be overlooking true confounding factors.

The true criticism of passive smoking remains—it is an unpleasant burden to impose on the nonsmoker.

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RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is ironic that whereas a few of us agonize over the question of whether active smoking is a major cause of lung cancer others seem willing to believe that passive smoking causes an appreciable incidence of lung and other cancers.

Sandler et al. (1) purport to have studied cancer risk in relation to "passive smoking in adulthood." They did not. They studied cancer cases in active and nonactive smokers in relation, mainly, to the smoking habits of the spouse. Two broad aspects were considered: whether or not the spouse "smoked regularly at any time during their marriage"; and, for dose-response relations, "the number of years of marriage during which a spouse smoked," or "the average amount smoked by spouse." Also, the "nonexposed group consisted of persons married to nonsmokers and persons who never married."

The smoking habits of the spouse are, however, a very poor surrogate for passive exposure to cigarette smoke. Thus, Repace and Lowrey (2) have estimated that the typical workplace exposure in the United States is about four times the typical exposure in the home. Matsukura et al. (3) found in Japan that the mean (\pm SE) urinary cotinine excretion for 200 nonsmokers living with no smokers in the home was 0.51 ± 0.09 μ g/mg of creatinine; for 272 nonsmokers with smokers in the home it was slightly higher, at 0.79 ± 0.10 (same units), but not significantly so.

The assumption by Sandler et al. that the smoking status of the spouse is a useful measure of exposure to ambient cigarette smoke is, therefore, highly suspect. This doubt is borne out by their own study of lung cancer cases in which "... there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose ..." (1). The observed cancer associations were

with the status of the spouse and not with exposure to cigarette smoke. That uncorrected confounding factors might have been present is further suggested by their finding of "statistically significant" associations "with several specific tumor sites ... including some which are not ordinarily regarded as smoking-related."

Assortative mating is a well established phenomenon that extends to the smoking habit (4) and hence we have to consider that the underlying factors leading to the choice of smoking/nonsmoking spouse might associate with the risk of certain cancers.

In principle, randomized trials can of course distinguish between causal, constitutional, and causal-plus-constitutional hypotheses of associations but they have yet to be conducted in connection with passive smoking. However, two important studies have been carried out, with randomization, in the context of active smoking (5, 6) and, because active smokers are inevitably passive smokers as well, the results of these trials are of immense importance not only to the findings of Sandler et al. but also to general theses about the carcinogenicity of mainstream and side-stream tobacco smoke.

We obtain the best available direct epidemiologic test of causal hypotheses by combining the results of the MRFIT in the United States (5) with those of the Whitehall Study in London (6). In the combined, low-smoking intervention groups some 56 cases of lung cancer (deaths in MRFIT, deaths and registrations in the Whitehall Study) were recorded in the total entry group of 7,142 men, a frequency of 0.78 per cent. For the combined, relatively high-smoking "usual care" groups the corresponding numbers were 53 in 7,169 or 0.74 per cent. Findings for all cancers other than lung cancer, several of which associate strongly with cigarette smoking, are astonishing. Some 88 cases, or 1.20

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Letters to the Editor

RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

It is unfortunate that Sandler et al. (1) did not obtain information on, or account for, additional possible confounding variables in their study. The only ones that they report having included were age, sex, race, active smoking, education, blue collar vs. white collar occupation, and parental smoking. We have found that the amount of passive smoking was correlated with self-reported exposure to occupational hazards, use of marijuana, and alcohol intake (2). Thus, for example, the increased risk of breast cancer observed by Sandler et al. may be due to increased alcohol intake (3) rather than to passive smoking. Perhaps exposure to occupational hazards explains the slightly increased risk of hematopoietic cancer (4) among passive smokers, and husbands' sexual behavior associated with the smoking habit (5) accounts for an increased risk of cervical cancer. The authors alluded to this last possibility, but did not rule it out.

Sandler et al. (1) were careful to point out that the associations that they found "... might relate to other factors we have not measured or to deficiencies in study design." However, they went on to state that they "have not been able to identify a possible confounder ... that could have caused the difference in smoking patterns of spouses between cases and controls." The above suggestions represent a few possibilities.

Sandler et al. also pointed out that sidestream smoke has higher concentrations of certain carcino-

gens than mainstream smoke. Nevertheless, because (a) the dosage of smoke is so much lower in passive than in active smoking, and (b) smokers also "passively" breathe sidestream smoke in addition to inhaling mainstream smoke, it would be surprising if passive smoking actually caused any cancers that were not associated with active smoking.

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RE: "PASSIVE SMOKING IN ADULTHOOD AND CANCER RISK"

Sandler et al. (1) removed much of the impropriety of their demonstration of an effect of passive smoking generally in raising the risk of cancer by focusing particular attention on the instances in which the study case was a nonsmoker. But substantial impropriety remains.

First, it gives cause to wonder how passive smoking could give rise to a doubled rate of cancer generally, including cancer of sites not previously associated with direct smoking of cigarettes. Those specific sites are only identified in their table giving results for nonsmokers plus smokers combined, with the added risk for passive smoking then shown at 60 per cent. The crude added risk of lung cancer from passive smoking, smokers plus nonsmokers combined, is shown as 90 per cent, but based on only 22 cases of lung cancer—of whom only two were nonsmokers. So only two nonsmoking lung cancer cases were available for judging the true effects of passive smoking on lung cancer.

Elsewhere (2), the study of passive smoking has focused specifically on lung cancer and specifically among individuals who themselves were nonsmokers, i.e., the nonsmoking wives of smokers, and, even so, such studies have been subject to criticism (3).

In Sandler et al. (1), the authors have given ostensible concern for potential confounding factors. Per-

haps others would agree that confounding factors have been taken into account, but not in my opinion. The issue of what is a confounding factor has become so confused that I have hesitated to get into the fray. I just look to see what is sensible. (Incidentally, the same issue of the *Journal* does carry an item (4) on confounding).

What the authors (1) treat as confounding factors are age (in broad age categories), sex, race, smoking (not relevant for the analysis on nonsmokers), three broad education groups, two broad occupation groups, and whether either parent smoked. Presumably, the factors adjusted for simultaneously in the analysis of passive smoking among nonsmokers are age, race, sex, and education.

But, somehow, I do not think of age as a confounding factor. Rather, it is a logical factor which must be taken into account in any reasonable analysis if one wants to come up with reasonable results. Much the same is true of race and sex, though I am less certain about level of education.

A truly confounding factor to my mind would be something like smoking and alcohol consumption. If heavy drinkers are also heavy smokers, sorting out their separate effects could be a problem. Anyway, if we are concentrating on passive smoking among non-

per cent, were recorded in the combined low-smoking intervention groups but only 60, or 0.84 per cent, in the high-smoking usual care groups. Is smoking prophylactic? Does quitting smoking result in changes of life-style that cause cancer? Or is this finding a wild, but acceptable, random excursion?

We may not be entitled to estimate confidence limits from this post hoc scrutiny but the results of these methodologically reputable randomized trials cast grave doubts on the validity of orthodox claims about the hazards of smoking. These claims derive, in the main, from case-control and prospective studies of self-selected smokers, ex-smokers and nonsmokers which, by their very nature, can tell us much about association but nothing about cause. The study of Sandler et al. (1) does not even tell us about associations with passive smoking; it does, however, shed some interesting light on cancer associations with the smoking/nonsmoking status of the spouse.

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THE AUTHORS REPLY

Friedman (1) and Mantel (2) have expressed some concerns about our passive smoking findings that are concerns for us as well (3). We agree that it would have been useful to have information on a greater number of potential confounding variables. Unfortunately, when conducting a study of many cancers, it is difficult to do justice to individual sites because risk factors vary widely by site.

While the possibility of confounding variables exists, some of those suggested by Friedman and Mantel are not likely to explain our findings. We collected information on alcohol consumption, and adjustment for alcohol intake did not alter our results. Marijuana use is also not likely to be a factor, since most of our cases were older than 40 years of age and from largely poor and rural areas. Occupational exposures may be important, although it is difficult to see how occupation of the subject would be associated with spouse's smoking, other than as an indicator of social class. Simple stratification into white and blue collar occupations did not change our results (3), and there were too few individuals with the same job for a more detailed analysis to be meaningful. Information on reproductive factors would have been useful and should certainly be included in subsequent studies given the observed associations with cancers of the breast and cervix. Since many of the factors thought to increase the risk of cervical cancer are thought to decrease the risk of breast cancer, however, it is not clear that those factors could explain our finding of elevated risk at both sites. Sexual behavior of husbands may also be important in cervical cancer risk, but reports suggest that this does not entirely explain the observed associations with spouse smoking (4, 5).

Burch points out that the smoking habits of the spouse may be a poor surrogate for passive smoke exposure (6). Certainly total passive smoke exposure

will be underestimated as Friedman's data suggest (7). However, Friedman's data and others suggest that individuals who live with smokers are likely to be more exposed to other people's cigarette smoke—either because they are more tolerant of other people's smoking or because they are often exposed to other smokers when in the company of their smoking spouse (7, 8). Thus while smoking by spouse may only roughly reflect the amount of tobacco smoke exposure, it appears to distinguish the most exposed from the least exposed. Misclassification of exposure is likely to dilute any association rather than create a spurious association, unless only controls who are married to nonsmokers are also exposed at work. Furthermore, one fourth of our cases and controls (35 per cent of the females) were either housewives or unemployed, and thus likely to receive most of their smoke exposure at home. For these subjects alone, the odds ratio associated with spouse's smoking was unchanged at 1.6.

As Mantel has pointed out, past studies of cancer risk from passive smoke exposure have focused on lung cancer risk among nonsmoking women married to smokers. Our study was not designed to focus on this issue, and with only 22 lung cancers, and only two among nonsmokers, we can add little to clarify results from those studies.

While it may be surprising that strong relative risks were seen for sites not generally associated with cigarette smoking, we believe that such effects are possible. Studies indicate that passive smoking has a pervasive biologic effect (8-12), making the boundaries between "smoking related" cancer sites and other sites unclear. Some sites may be considered unrelated to cigarette smoke because risks are less dramatic than those for other sites, or because studies have not been done. While active smokers are also passive smokers, if an effect were due to some specific property of the side-

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